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Case Report

Opioid-induced hyperalgesia—worsening pain in opioid-dependent patients☆

Abstract

Patients with chronic opioid use are commonly treated in the emergency department (ED). Opioid-induced hyperalgesia occurs in patients consuming opioids chronically and is a paradoxical response of increased pain with opioid administration. It is difficult to diagnose and is often underrecognized, and therapies are unconventional. We report a case of a young service member with chronic pain and opioid use who presented to the ED with opioid-induced hyperalgesia.

A 23-year-old male US service member presented to the emergency department (ED) with severe pain in his left leg and perineum. The patient had a history of bilateral above-the-knee amputations (AKAs) and a severe abdominoperineal injury sustained after trauma 8 months prior in Afghanistan. His pain had been chronic since his amputations and had progressively worsened over the last 3 days since his primary care manager discontinued his hydromorphone, reduced his fentanyl patch from 100 μg to 75 μg/h and started buprenorphine 2 mg sublingual 4 times daily. He reported nausea and chills but denied fever, abdominal pain, dysuria, or other symptoms. His medical history was significant for posttraumatic stress disorder, anxiety, chronic pain, phantom limb pain, insomnia, and depression. Surgeries included bilateral AKA, left index finger amputation, colostomy, and abdominoperineal revision. He denied alcohol intake, tobacco use, or substance abuse. He had no known drug allergies. His initial vital signs were blood pressure of 137/75 mm Hg, pulse rate of 75 beats per minute, 16 respirations per minute, temperature of 37°C, pulse oximetry 97%, and pain score of 10/10. On examination, he was alert, anxious, and in moderate distress and manifested no yawning, sweating, lacrimation, rhinorrhea, mydriasis, or piloerection. His abdomen was soft, nontender, and had a functioning left lower quadrant colostomy with no signs of infection. He had bilateral AKAs without signs of infection. The remainder of the examination was unremarkable. Hydromorphone 1 mg IV was infused without improvement of symptoms. Thirty minutes later, hydromorphone was repeated; however, the patient reported that his pain increased. He then received ketorolac 30 mg IV. We called his primary care manager who stated that the patient's pain specialist had diagnosed him with opioid-induced hyperalgesia (OIH). After consultation with the Hospital Pain Service attending physician, the patient was admitted under the care of the pain service to the intensive care unit to receive a ketamine infusion to treat his OIH.

Prescription opioid medication use and ED visits for pain are common. OIH is a paradoxical condition wherein patients receiving opioids experience an increased perception of pain [1,2]. Basically, pain sensitivity rises with opioid dose. Although OIH has been described since 1880, the incidence of OIH is unknown, and the diagnosis is difficult and underrecognized. Patients present with worsening pain despite escalating analgesic doses, pain not explained by progression of the underlying injury, generalized pain, pain at sites distant from the injury, or excessive pain from surgical procedures [1,3]. OIH generally occurs following long-term, high-dose opioid use, with morphine being the most common agent. OIH may develop in opioid-dependent patients and in patients receiving short courses of opioid analgesics during or after surgery [1]. OIH has been described in healthy volunteers, in chronic pain patients, and with administration of either low or high opioid doses [3]. The differential diagnosis includes disease progression, opioid tolerance, physical dependence or withdrawal, addiction, and abuse. On opioid administration, pain will worsen in OIH. With opioid addiction, pain may improve, but overall function may worsen [2].

The primary mechanism for OIH may involve enhanced neuronal stimulation in relation to opioid use [4]. The glutaminergic system involves N-methyl-D-aspartate (NMDA), an excitatory neurotransmitter [5]. Increased spinal dynorphin levels cause the release of spinal excitatory neuropeptides. Descending pain facilitation pathways become activated. Finally, polymorphisms of catechol-O-methyltransferase modulate pain response by altering levels of synaptic dopamine and noradrenalin, resulting in increased stimulation. Treatment options include opioid switching, nonopioid analgesics, and adjuvant analgesics. Opioid antagonists do not reverse the

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hyperalgesia [2]. Opioid "switching" is introducing another opioid at a lower equianalgesic dose while decreasing the original opioid dose [2,5]. Nonopioid analgesics that are used include nonsteroidal anti-inflammatory drugs, α-2 agonists, and amantadine. α-2 Agonists act centrally and peripherally and have been shown to reduce pain. Amantadine is an NMDA receptor antagonist that may mitigate central sensitization.

Adjuvant analgesics may lessen nociceptive sensitization and reduce the required opioid dose administered [3,5]. Ketamine, an NMDA receptor antagonist, produces analgesia, sedation, and amnesia. Newer uses include ketamine as an antihyperalgesic, a component of opioid withdrawal treatment, and for reversal of opioid tolerance. It is thought that ketamine binds inside the ion channel at the phencyclidine binding site and blocks calcium influx, thus preventing subsequent depolarization and excitation [6]. Calcium channel activation contributes largely to the "wind up" phenomenon leading to central sensitization [5,7]. Blocking this response may ultimately result in decreased pain. A low-dose ketamine infusion is often used.

Patients with chronic opioid use are commonly treated in the ED. Opioid-induced hyperalgesia occurs after chronic opioid use and is a paradoxical response of increased pain with opioid administration. It is difficult to diagnose and is often underrecognized. Treatment involves a multimodal approach including opioid dose reduction, opioid switching, and adjunctive analgesics such as ketamine.

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